Appendix VI

POLICY OF THE NATIONAL CANCER INSTITUTE FOR DATA AND SAFETY MONITORING OF CLINICAL TRIALS

Introduction

All clinical trials supported or performed by NCI require some form of monitoring. The method and degree of monitoring should be commensurate with the degree of risk involved in participation and the size and complexity of the clinical trial. Monitoring exists on a continuum from monitoring by the principal investigator/project manager or NCI program staff to a data and safety monitoring board (DSMB). These monitoring activities are distinct from the requirement for study review and approval by an Institutional Review Board (IRB).

Throughout this policy, the term "awardee" means the awardee institution. In the case of NCI intramural research, the comparable institutional unit is the NCI.

Responsibility for Data and Safety Monitoring

Responsibility for data and safety monitoring depends on the phase of the study and may be conducted by NCI program staff or contractor, by the principal investigator/project manager conducting the study, or by a DSMB. Regardless of the method used, monitoring must be performed on a regular basis. Oversight of the monitoring activity is the responsibility of NCI program staff. In the case of extramurally funded research, adherence to this NCI policy and any data and safety monitoring policies of the NCI Division making the award will be made a condition of the award.

Phase I and Phase II studies may be monitored by the principal investigator/project manager, by NCI program staff or a designee, or jointly. When conducted by the principal investigator/project manager, the awardee must have written policies and procedures describing the monitoring and reporting processes in place. The awardee's policies must be consistent with any policies of the NCI Division making the award. NCI program staff from the awarding NCI division will determine the acceptability of the awardee's policies and procedures. These will be documented in the grant, cooperative agreement or contract file and become part of the award.

All Phase III randomized clinical trials supported or performed by NCI require monitoring by a DSMB. The organization, responsibilities, and operation of the DSMB are described below.

For studies co-funded with other NIH Institutes or Centers (IC), the lead NIH IC will be responsible for monitoring the study and establishing a DSMB if necessary. Oversight of the DSMB will be the collaborative responsibility of the lead NIH IC and NCI.

Requirement for Data and Safety Monitoring Boards

Data and Safety Monitoring Boards must be established to monitor all Phase III randomized clinical trials supported or performed by NCI. Funds to support the functions and operations of the DSMBs will be provided by NCI in a fashion to be determined by each NCI Division.

Responsibilities of the DSMB

- Familiarize themselves with the research protocol(s) and plans for data and safety monitoring.

- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data. The DSMB reviews trial performance information such as accrual information. The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- Review reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial. A copy of this information will be provided to the NCI Division Director or designee. The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRBs.

Membership

The DSMB voting members will be appointed for a fixed term by the principal investigator/project manager or designee. Proposed DSMB members must be reviewed and approved by the awarding NCI Division Director or designee prior to their appointment. The Chair of the DSMB will be selected from among the voting members. Voting members of the DSMB should include physicians, statisticians, other scientists, and lay representatives selected based on their experience, reputation for objectivity, absence of conflicts of interest (and the appearance of same), and knowledge of clinical trial methodology. Program and statistical staff from the NCI will be permitted to serve as non- voting *ex officio* members of the DSMB at the request of the NCI Program Director.

Voting members may be from within or outside the institution[1], but a majority should not be affiliated with the institution. Staff affiliated with the institution who are members of the DSMB should view themselves as representing the interest of patients and not that of the institution. Voting members directly involved with the conceptual design or analysis of a particular trial must excuse themselves from all DSMB discussion of the particular trial and must not receive that portion of the DSMB report

related to the particular trial.

Meetings

DSMB meetings will be held at least annually and more often depending on the nature and volume of the trials being monitored. Each meeting should be divided into three parts. First, an open session in which members of the clinical trial team may be present, at the request of the DSMB, to review the conduct of the trial and to answer questions from members of the DSMB. The focus in the open session may be on accrual, protocol compliance, and general toxicity issues. Outcome results must not be discussed during this session. Following this session, a closed session involving the DSMB members and the coordinating center/statistical office statistician(s) handling the trial should be held. The statistician(s) should present and discuss the outcome results with the DSMB. A final executive session involving only DSMB members should be held to allow the DSMB opportunity to discuss the general conduct of the trial and all outcome results, including toxicities and adverse events, develop recommendations, and take votes as necessary.

A written report containing the current status of each trial monitored, and when appropriate any toxicity and outcome data, should be sent to DSMB members by the coordinating center/statistical office allowing sufficient time for the DSMB members to review the report prior to the meeting. This report should address specific toxicity concerns as well as concerns about the conduct of the trial. The report may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow up.

Recommendations from the DSMB

DSMB recommendations should be based on results for the trials being monitored as well as on data available to the DSMB from other studies. It is the responsibility of the coordinating center/statistical office, trial investigator(s), NCI program staff and statisticians, and individual DSMB members to ensure that the DSMB is kept apprised of non-confidential results from other related studies that become available, and of any programmatic concerns related to trials being monitored. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to specific trials.

DSMB recommendation(s) will be given to the trial principal investigator/project manager[2] with a copy provided to the NCI Division Director or designee. If the DSMB recommends a study change for patient safety or efficacy reasons, or that a study be closed early due to slow accrual, the trial principal investigator/project manager must act to implement the change as expeditiously as possible. In the unlikely situation that the trial principal investigator/project manager does not concur with the DSMB, then the NCI Division Director or designee must be informed of the reason for disagreement. The trial principal investigator/project manager, DSMB Chair, and the NCI Division Director or designee will be responsible for reaching a mutually acceptable decision about the study. Confidentiality must be maintained during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and NCI staff to seek advice to assist in reaching a mutually acceptable